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(54) Stabilized pharmaceutical compositions containing derivatives of vitamins D2 and D3.

(57) 1. A solid state pharmaceutical composition which comprises at least ingredients (a), (b) and (c) of the following ingredients (a), (b), (c) and (d), namely:

(a) at least one active component selected from pharmaceutically active derivatives of vitamin D2 and vitamin D3;

(b) at least one pharmaceutically acceptable antioxidant;

(c) at least one pharmaceutically acceptable polyoxyalkyl stabilizer;

(d) at least one solid pharmaceutical excipient or carrier in an amount sufficient to impart the characteristics of a solid to the composition.

EP 0 588 539 A1

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to stabilized solid state pharmaceutical compositions containing an active component selected from pharmaceutically active derivatives of vitamin D_2 and vitamin D_3.

Derivatives of vitamin D_2 and vitamin D_3, which generally possess at least the activity of their underivatized precursors, have been found to be useful in medicine, e.g. they increase the serum calcium level, inhibit parathyroid hormone, and affect bone formation; they may also inhibit the proliferation of psoriatic and certain cancer cells. In particular, they are used to treat symptoms such as chronic renal failure, hypoparathyroidism, vitamin-D-resistant rickets, osteomalacia, osteoporosis and psoriasis.

However, such derivatives have the disadvantage of low stability under ordinary storage conditions. Moreover, refrigeration, protection against actinic radiation and replacement of the ambient atmosphere have not been found to be satisfactory as a means of stabilization and are often costly. Consequently, various stabilization methods have been proposed. Thus, by way of example, EP 413828A teaches dispersion of active ingredient in an excipient readily soluble in organic solvent and a basic substance, EP 387808A uses a stabilizer selected from polyvinylacetal diethylaminoacetate and hydroxypropylcellulose, while JP 258722/91 discloses compositions containing crystalline cellulose and butylated hydroxytoluene (BHT) or butylated hydroxyanisole (BHA), as antioxidant. JP 074123/92 discloses compositions containing active forms of vitamin D_3 and gelatin in the same phase; in an example of a liquid phase composition, a polyoxyethylene hardened castor oil derivative was also present.

All of these exemplary solid pharmaceutical compositions show unsatisfactory stability at elevated temperatures or/and humidities. Consequently, there is a great need for improved stabilized solid state pharmaceutical compositions containing the ingredients referred to above.

Accordingly, it is an object of the invention to provide solid pharmaceutical compositions containing an active component selected from pharmaceutically active derivatives of vitamin D_2 and vitamin D_3, which exhibit improved stability for a prolonged period of time. Other objects of the invention will appear from the description which follows.

SUMMARY OF THE INVENTION

The present invention accordingly provides in one aspect, a solid state pharmaceutical composition which comprises at least ingredients (a), (b) and (c) of the following ingredients (a), (b), (c) and (d), namely: (a) at least one active component selected from pharmaceutically active derivatives of vitamin D_2 and vitamin D_3; (b) at least one pharmaceutically acceptable antioxidant; (c) at least one pharmaceutically acceptable polyoxyalkyl stabilizer; (d) at least one solid pharmaceutical excipient or carrier in an amount sufficient to impart the characteristics of a solid to the composition.

In another aspect, the present invention provides a process for preparing the pharmaceutical composition as defined in the preceding paragraph, which comprises the sequential steps of: (i) dissolving ingredients (a) and (b) in a solvent; (ii) thoroughly mixing the solution formed in step (i) with ingredients (c), and with ingredient (d) when this is present; and (iii) removing the solvent.

DETAILED DESCRIPTION OF THE INVENTION

The product of the process just described may be granulated; if desired, the granulate may then be formed into a dosage form selected from tablets, sachets and gelatin capsules (e.g. hard gelatin capsules). A lubricant such as magnesium stearate and/or calcium stearate may be added at any convenient stage. It will be appreciated that in the alternative, the product of the process described above need not be granulated, but may be obtained as a uniform dry powder, which is then mixed with lubricant if desired, and then made into dosage forms such as those specified above. In order to avoid premature deterioration of the composition, it is preferred to remove the solvent under mild conditions, e.g. at ambient temperature, and in the presence of an inert atmosphere (such as nitrogen) or in vacuum.

Presently preferred ingredients of the solid state pharmaceutical composition of the invention are:

(a) 1α-hydroxycholecalciferol (1α-(OH)D_3), 24-hydroxycholecalciferol (24-(OH)D_3), 25-hydroxycholecalciferol (25-(OH)D_3),1α,25-dihydroxycholecalciferol (1α,25-$(OH)_2D_3$), 1α,24-dihydroxycholecalciferol (1α,24-$(OH)_2D_3$), 24,25-dihydroxycholecalciferol (24,25-$(OH)_2D_3$), 1,24,25-trihydroxycholecalciferol (1,24,25-$(OH)_3D_3$), 1α-hydroxyergocalciferol (1α-(OH)D_2) and 1α,25-dihydroxyergocalciferol (1α,25-$(OH)_2D_2$);

(b) butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), vitamin E, propyl gallate, β-carotene and ascorbic acid;

(c) polyethyleneglycols, polyethyleneglycol ethers, polyethyleneglycol esters, polyoxyethylated castor oil, polyoxyethylated hydrogenated castor oil (e.g. Cremophor RH, a Trade Mark of BASF AG), polyoxyethylated sorbitan fatty acid esters and polyoxyethylated glycerol fatty acid esters;

(d) lactose, sorbitol and calcium phosphate.

As regards the proportions of the ingredients which may be used in the solid state pharmaceutical compositions of the invention, it will be evident that since use of a pharmaceutical excipient or carrier, i.e. optional ingredient (d), is conventional, the proportions in which it may be used, if desired, in the present invention are also conventional. The essential ingredients (a), (b) and (c) may be used in proportions which may be varied within wide ranges.

Active ingredient (a), when used in a composition of the invention intended for direct therapeutic application (in the usual dosage forms), may be present in an amount within the range of e.g. 0.0000025 to 5.0 wt.%, but more usually 0.0005 to 1.0 wt.%. However, it is also within the contemplation of the present invention that the compositions may be in the form of concentrates of active ingredient, prior to preparation of finished dosage forms, in which case up to 25, or even up to 50 wt% of ingredient (a), may be present.

Antioxidant ingredient (b) may be present in an amount within the range of e.g. 0.0000025 to 10.0 wt.%, but more usually 0.0025 to 1.0 wt.%. As is of course well known in the pharmaceutical art, the amount of antioxidant used Will also take account of the relative toxicity of a particular antioxidant.

Polyoxyalkyl stabilizer, ingredient (c), may be present in an amount within the range of e.g. 0.01 to 50 wt.% in a composition intended for therapeutic administration. In this connection, reference may be made the Examples set forth below in which the amount of ingredient (c) varies between 3 and more than 21 wt.% of the total composition. However, as may also be seen from the Examples, the proportion of ingredient (c) may approach 100%, when ingredient (d) is omitted.

It is presently preferred that, when ingredient (d) is present, the compositions comprise (by weight) 0.00003 to 0.8% (a), 0.01 to 0.1% (b) and 0.03 to 30% (c); and corresponding relative proportions of (a), (b) and (c), when ingredient (d) is absent. In other words, according to a presently preferred embodiment, the relative weight ratio ranges of ingredients (a), (b) and (c) are 0.00003 to 0.8 (a) : 0.01 to 0.1 (b) : 0.03 to 30 (c), respectively, whether or not ingredient (d) is present.

The invention will now be illustrated by the following non-limitative Examples. It may be noted in passing that the invention includes additionally the compositions specified in Examples 1-5, but from which the excipients (lactose or sorbitol) and lubricant (magnesium stearate) have been excluded.

EXAMPLE 1

Butylated hydroxyanisole (557 mg) and 1α-OH-D_3 (5.1 mg) were dissolved in ethanol (300 g). The solution was mixed for 20 minutes with sorbitol (1.8 kg) and polyoxyethylated hydrogenated castor oil (55.69 g) in a high speed mixer, the residual ethanol solution being washed into the mixer with an additional 50 g ethanol. The resulting wet mass was removed and dried on trays under vacuum with a nitrogen bleed at ambient temperature, to give dry granules which were screened (30 mesh) and mixed with magnesium stearate (4.64 g). These granules can be packed into sachets or hard gelatin capsules, or pressed into tablets, by conventional methods. The product contained the ingredients in the following percentages by weight:

polyoxyethylated hydrogenated castor oil	2.99 %
1α-OH-D_3	0.00027%
butylated hydroxyanisole	0.0299 %
sorbitol	96.73 %
magnesium stearate	0.25 %

Examples 2-5 were carried out similarly (except where indicated), but contained the ingredients as described below, in which the stated percentages are by weight.

EXAMPLE 2

In this Example, the lactose and magnesium stearate are omitted prior to the drying step. The lactose- and magnesium stearate-free product is then thoroughly mixed with these two ingredients prior to tabletting.

polyethylene glycol 6000	21.25 %
24,25$(OH)_2D_3$	0.011%
butylated hydroxyanisole	0.04 %
lactose	78.47 %
magnesium stearate	0.25 %

EXAMPLE 3

polyoxyethylated hydrogenated castor oil	3.0 %
24,25$(OH)_2D_3$	0.088%
butylated hydroxyanisole	0.03 %
sorbitol	96.63 %
magnesium stearate	0.25%

EXAMPLE 4

polyoxyethylated hydrogenated castor oil	3.0 %
24,25$(OH)_2D_3$	0.01 %
butylated hydroxyanisole	0.03 %
sorbitol	96.71 %
magnesium stearate	0.25%

EXAMPLE 5

polyoxyethylated hydrogenated castor oil (Cremophor RH40)	4.0 %
1α-OH-D_3	0.000373%
butylated hydroxyanisole	0.04 %
sorbitol	95.96 %

STABILITY TESTS

The exemplified solid state pharmaceutical compositions in tablet form were stored at 40 °C and 75% relative humidity. Assay of the active ingredient at monthly intervals gave the following results, expressed as a percentage of the initial assay.

Months	Example 1	Example 2	Example 3	Example 4
0	100.0	100.0	100.0	100.0
1	105.0	-	99.1	100.0
2	101.7	-	95.9	102.0
3	98.98	91.3	96.0	98.8
4	102.0	-	98.2	97.4
5	98.15	-	-	-
6	99.2	-	91.2	95.1

The excellent results of stability tests shown above by solid state pharmaceutical compositions in accordance with the present invention may be contrasted with the above-mentioned prior art, which may be

summarized as follows, from which it may also be noted that no results were given for any period of time longer than one month.

EP 413828A: at 40 °C and 75% relative humidity (as in the present stability tests), assay was 95-100% at 7 days, 93-99% at 14 days and 91-94% at 30 days.

EP 387808A: at 50 °C, assay was 98.0-98.8% at two weeks and 95.7-97.5% at four weeks.

JP 258722/91: after one month at 40 °C, assayed 97.82 or 97.18% vitamin D_3, which is not directly comparable with the present active compounds (data on exemplified 1α-OH-D_3 not supplied).

JP 074123/92: after 7 and 14 days at 60 °C, a liquid phase composition assayed 95.4 or 81.7% 1α-OH-D_3.

It will be appreciated by persons skilled in the art that the present invention is not restricted to the embodiments which have been particularly described hereinabove, but that many modifications and variations may be made. Thus, the invention may be practised in accordance with its scope, concept and spirit, as will be appreciated by skilled persons, after reading the present specification and the appended claims.

Claims

1. A solid state pharmaceutical composition which comprises at least ingredients (a), (b) and (c) of the following ingredients (a), (b), (c) and (d), namely:
   (a) at least one active component selected from pharmaceutically active derivatives of vitamin D_2 and vitamin D_3;
   (b) at least one pharmaceutically acceptable antioxidant;
   (c) at least one pharmaceutically acceptable polyoxyalkyl stabilizer;
   (d) at least one solid pharmaceutical excipient or carrier in an amount sufficient to impart the characteristics of a solid to the composition.

2. A pharmaceutical composition according to claim 1, wherein ingredient (a) is selected from 1α-hydroxycholecalciferol, 24-hydroxycholecalciferol, 25-hydroxycholecalciferol, 1α,25-dihydroxycholecalciferol, 1α,24-dihydroxycholecalciferol, 24,25-dihydroxycholecalciferol, 1,24,25-trihydroxycholecalciferol, 1α-hydroxyergocalciferol and 1α,25-dihydroxyergocalciferol.

3. A pharmaceutical composition according to claim 1, wherein ingredient (a) is selected from 1α-hydroxycholecalciferol and 24,25-dihydroxycholecalciferol.

4. A pharmaceutical composition according to any of the preceding claims, wherein ingredient (b) is selected from butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), vitamin E, propyl gallate, β-carotene and ascorbic acid.

5. A pharmaceutical composition according to any of the preceding claims, wherein ingredient (c) is selected from polyethyleneglycols, polyethyleneglycol ethers, polyethyleneglycol esters, polyoxyethylated castor oil, polyoxyethylated hydrogenated castor oil, polyoxyethylated sorbitan fatty acid esters and polyoxyethylated glycerol fatty acid esters.

6. A pharmaceutical composition according to any of the preceding claims, wherein ingredient (d) is present, and is selected from lactose, sorbitol and calcium phosphate.

7. A pharmaceutical composition according to any of the preceding claims, which contains additionally a lubricant.

8. A pharmaceutical composition according to claim 7, wherein the lubricant is selected from magnesium stearate and calcium stearate.

9. A pharmaceutical composition according to any of the preceding claims, wherein the relative weight ratio ranges of ingredients (a), (b) and (c) are 0.00003 to 0.8 ingredient (a) : 0.01 to 0.1 ingredient (b) : 0.03 to 30 ingredient (c), respectively.

10. A pharmaceutical composition according to any of the preceding claims, which is in a form selected from powdered and granulated form.

11. A pharmaceutical composition according to any of the preceding claims, which is constituted in a dosage form selected from tablets, sachets and gelatin capsules.

12. A process for preparing the solid state pharmaceutical composition as defined in claim 1, which comprises the sequential steps of:

(i) dissolving ingredients (a) and (b) in a solvent;

(ii) thoroughly mixing the solution formed in step (i) with ingredient (c), and with ingredient (d) when this is present; and

(iii) removing the solvent.

13. Process according to claim 12, wherein step (iii) is carried out at ambient temperature, in an inert atmosphere or in vacuum.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number EP 93 30 6978

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X Y	WO-A-9 209 271 (SUMITOMO PHARMACEUTICALS CO., LTD.) * page 3, paragraph 2 * * page 4, paragraph 3 * * page 6 - page 7 *	1-8,10,11 9,12,13	A61K31/59 A61K9/20
X Y	WO-A-9 116 899 (SUMITOMO PHARMACEUTICALS CO., LTD.) * page 3, paragraph 4 * * page 4, paragraph 4 * * page 5, paragraph 4 - page 7, paragraph 2 *	1-8,10,11 9,12,13	
X	EP-A-0 215 596 (TEIJIN LIMITED) * page 2, line 44 - page 3, line 40 *	1-5	
X	EP-A-0 177 920 (TEIJIN LIMITED) * page 5, line 12 - page 8, line 34 *	1-5	
X	US-A-3 932 634 (JOSEPH A. KARDYS) * column 1, line 50 - column 2, line 68; example 1 *	1,5	TECHNICAL FIELDS SEARCHED (Int. Cl.5)
Y	DD-A-266 099 (VEB JENAPHARM) * the whole document *	1-13	A61K
Y	Week 9204, Derwent Publications Ltd., London, GB; AN 92-030616 & JP-A-3 279 324 (OTSUKA PHARM KK) 10 December 1991 * abstract *	1-13	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	05 JANUARY 1994	TZSCHOPPE D. A.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)

Vitamin D and calcium compsn. in single tablet form - comprises active principles, dry and wet binder, lubricant, diluent and sweetening binder, useful for treating osteoporosis

Patent Assignee: LAB INNOTHERA SA (INNO-N); LAB INNOTHERA (INNO-N)

Inventor: MEIGNANT C; STENGER E

Number of Countries: 056 Number of Patents: 013

Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Main IPC	Week
WO 9609036	A1	19960328	WO 95FR1053	A	19950804	A61K-009/00	199619 B
FR 2724844	A1	19960329	FR 9411381	A	19940923	A61K-033/10	199620
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ES 2131845	T3	19990801	EP 95927758	A	19950804	A61K-009/00	199937

Priority Applications (No Type Date): FR 9411381 A 19940923

Cited Patents: 413828

Patent Details:

Patent	Kind	Lan	Pg	Filing Notes	Application	Patent
WO 9609036	A1	F	16			

Designated States (National): AU BG BR BY CA CN CZ EE FI GE HU IS JP KG KP KR KZ LR LT LV MD MN MX NO NZ PL RO RU SG SI SK TJ TM UA UG US UZ VN

Designated States (Regional): AT BE CH DE DK ES FR GB GR IE IT LU MC NL OA PT SE

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AU 9531683	A		Based on	WO 9609036
DE 29521515	U1	16	Application no.	WO 95FR1053
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Designated States (Regional): AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

JP 10505850	W	17	Based on	WO 9609036
HU 77702	T		Based on	WO 9609036
KR 97705975	A		Based on	WO 9609036
EP 785769	B1	F	Based on	WO 9609036

Designated States (Regional): AT BE CH DE DK ES GB GR IE IT LI LU MC NL PT SE

DE 69508263	E	Based on	EP 785769
		Based on	WO 9609036
ES 2131845	T3	Based on	EP 785769

Abstract (Basic): WO 9609036 A

Therapeutic compsn. of vitamins and calcium, in the form of tablets, comprises: elemental calcium, at least one D vitamin, at least one dry and wet binder synergistically combined with at least one diluent, at least one binder and at least one diluent, at least one of which is a sweetener. Also claimed is the prepn. of the above compsn. comprising: (i) granulating elemental calcium with the dry and wet binder; (ii) premixing vitamin D with the sweetening binder; (iii) mixing a sweetening diluent, a supplementary sweetening binder and a flavouring with the prods. from (i) and (ii), whilst adding a lubricant; and (d) forming tablets from the mixt., using a rotary press.

USE - The compsn. is used to combat osteoporosis (claimed).

ADVANTAGE - Vitamin D and calcium can be combined in optimal and specific dosages.

Dwg.0/0

Derwent Class: A96; B01; B05; B06

International Patent Class (Main): A61K-000/00; A61K-009/00; A61K-009/20; A61K-033/06; A61K-033/10

International Patent Class (Additional): A61K-031/59; A61K-033/42; A61K-031-59; A61K-033/10